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Dated: September 24, 2008 Signature: _____ (Max D. Hensley)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of	)	Group Art Unit: 1657
Mark W. Becker	)	Attorney Docket No. 249.P2
	)	Examiner: Paul C. Martin
Serial No: 10/785,497	)	
Filed: February 24, 2004	)	
Title: Prodrugs of Phosphonate Nucleotide Analogues and Methods for Selecting and Making Same	)	

APPEAL BRIEF UNDER 37 CFR 41.37

Applicants hereby appeal from the Examiner's Final Rejection of all the claims in this case. Applicants submitted a Notice of Appeal from the Final Rejection on April 4, 2008. A Request for a Four Month Extension of Time is submitted herewith, whereby the period for filing the Brief is extended until October 4, 2008. Fees for the Brief and the Extension of Time are submitted herewith.

Real Party In Interest

The real party in interest is Gilead Sciences, Inc.

Related Appeals and Interferences

None

Status of Claims

Claims 1, 3-13 and 15-17, all the claims now pending, were Finally Rejected in the Office rejection mailed Oct. 24, 2007. Claims 2, 14 and 18 have been canceled.

Status of Amendments

All of Applicants' amendments have been entered.

Summary of Claimed Subject Matter

The subject matter of claim 1, the sole independent claim in this case, is based on applicants' observation that the activity of prodrugs of methoxyphosphonate nucleotide analogues will vary depending upon the tissues to which they are administered. See specification pages 10-15. Thus, the claimed process is directed to a method for identifying prodrugs of methoxyphosphonate nucleotide analogues that are selectively metabolized in a given target tissue to the active parental drug, as measured by the resulting antiviral or antitumor activity. In accordance with the inventive method, one begins by selecting a tissue where antiviral or antitumor activity is desired (the "target tissue") and one where it is not (the "non-target tissue"), administering the prodrug, and determining the relative activity in the two tissues. The desired prodrug is the one which produces comparably greater activity in the target tissue as compared to the non-target tissue.

Grounds of Rejection to be Reviewed on Appeal

Applicants respectfully request review of all three grounds of rejection now outstanding. These are the rejection of claims 1, 3-7 and 10-13 under 35 USC 103(a) as being unpatentable over Shaw et al., the rejection of claims 1, 3 -7, 9 – 13, 15 and 16 under 35 USC 103(a) as being unpatentable over Shaw et al. in view of Glazier et al., and the rejection of claims 1, 3 – 8, 10 – 13 and 17 under 35 USC 103(a) as being unpatentable over Shaw et al. in view of Starrett et al.

Argument

The rejection of claims 1, 3-7 and 10-13 under 35 USC 103(a) as being unpatentable over Shaw et al. should be reversed because Shaw et al. lacks the claimed element "target tissue" and the rejection is devoid of any reasonable basis for modifying Shaw to supply this missing element.

According to the examiner's original statement of the rejection, Shaw teaches a screening method comprising providing a prodrug of PMPA (this is a methoxyphosphonate nucleotide analogue), selecting plasma as a target tissue and intestine and liver homogenate as non-target tissue, administering prodrug to all "tissues" and determining the relative *in vitro* biological stability and bioavailability of the PMPA in the tissues. In the Final Rejection the examiner conceded that plasma is not a target tissue, as that term is defined in specification page 11, lines 14-16, but instead advanced the proposition that the artisan would have used blood in place of plasma because esterolytic degradation would have been "the same" as in whole blood.

The Examiner in the Advisory Action urges that the Office does not have to provide references to support this argument (i.e., that blood would have been considered equivalent to plasma in the Shaw method) "as long as the basis for rejection is either a fact and/or technical reasoning to (sic) reasonably support the determination of obviousness" (page 2). The "fact" or "technical reasoning" relied on by the Examiner is that esterolytic degradation would be the equivalent between plasma and whole blood.

Shaw et al. were concerned with determining oral bioavailability of certain methoxyphosphonate prodrugs. Oral bioavailability studies are used to determine the ability of a compound to be orally absorbed through the gut. They are not intended to determine relative activity of a drug among various tissues. As such, the relevance of Shaw et al. to the claims is one of "accidental" obviousness since Shaw et al. and the present inventors had entirely different objectives.

While the presence of differing intent between a claimed invention and a reference is not enough to make an otherwise anticipated or obvious combination patentable, it is important to consider intent or objectives in analyzing whether any changes in the reference required to reach the pending claims would have been obvious to the ordinary artisan. Stated differently, it is important to focus on the reference procedures and objectives, avoiding modifications to those procedures that would have been unobvious but are in fact guided by hindsight analysis of applicants' invention.

Shaw et al. conducted an *in vitro* study and an *in vivo* study. In the *in vivo* study (pages 1825-1826) Shaw et al. orally administered the candidate prodrugs to dogs, recovered blood at various time points after administration, centrifuged the blood to remove cells (to make plasma) and determined the amount of converted prodrug (i.e., activity of the prodrug) in the plasma. This study clearly does not meet the features of the claims because it fails to conduct any comparative studies of activity in different tissues.

Shaw et al. also conducted an *in vivo* study (pages 1824-1825), and it is this one that the Examiner appears to be relying upon. In this study, Shaw et al. investigated the biological stability of the prodrugs in dog plasma, intestinal homogenate and liver homogenate. The plasma was a commercial pooled dog plasma that did not originate from blood treated with the prodrugs. In this study each of the prodrugs were added to the plasma and homogenates, incubated and then the amount of conversion of each prodrug to parental drug (activity) was determined. These studies offered an inferential understanding of the conversion of the prodrugs during intestinal absorption through the hepatic metabolism stage.

The Shaw et al. *in vitro* method fails to disclose the "target tissue" feature of claim 1 et seq. Plasma is not a tissue, which the examiner recognizes, and claim 1 excludes intestinal homogenate as a tissue. Instead the examiner takes the position that it would have been obvious to use blood instead of plasma, arguing that blood contains esterolytic enzymes just like plasma, and that this is a "fact" applicants should recognize. The examiner is taking the position that "as plasma is blood plasma with the cells removed (monocytes, macrophages, etc.) but with the enzyme components remaining, one of ordinary skill in the art would have concluded that the

degradation observed in plasma would have been the same as in whole blood" (Advisory Action, page 2).

This is a whole cloth argument not based on any cited reference, and is clearly groundless. First, the enzyme complement of plasma per se is not the same as blood because the heparin added to anticoagulate the blood (see Shaw et al. "heparinized tubes", page 1826) inhibits blood clotting enzymes. Even if the esterolytic enzymes of plasma were the same as the enzymes in the non-cellular component of blood, blood cells such as moncytes, red blood cells and the like contain a unique complement of esterolytic enzymes. Phagocytes alone contain a diverse collection of lysozomal enzymes designed to digest waste matter and invading organisms, none of which enzymes by definition is found in plasma. Blood certainly would not be considered esterolytically "equivalent" to plasma by any stretch of the imagination, and the examiner has not cited any reference teaching or suggesting a foundation for this proposition.

Regardless, the claims also distinguish Shaw et al. by excluding intestine as a target tissue. Shaw et al. are devoid of any teaching or suggestion to omit intestinal homogenate from their study. On the contrary, intestine is critical to their work because it is a critical participant in oral absorption/hydrolysis of prodrugs. It would have been inconceivable for Shaw et al. to omit the study of intestinal homogenate. Applicants' specification observes that intestine is not a preferred target tissue (specification page 11, lines 14 – 16), in keeping with the intent stated in the specification to exclude conventional bioavailability studies from the scope of the claims.

In the Advisory Action the examiner observes that even if intestinal homogenate was omitted from the Shaw et al. method the resulting method would meet the claims (plasma "target tissue" and liver homogenate as the "non-target tissue"). This begs the question of why one skilled in the art would want to omit the portion of the Shaw et al. method that uses intestinal homogenate.

Claim 10

Claim 10 is particularly patentable over Shaw et al. Administration of the prodrugs to live dogs in the Shaw et al. *in vivo* method does not render claim 10 obvious. Shaw et al. were simply determining the ability of the prodrug to produce active drug in the circulation after oral administration. Shaw et al. do not disclose assaying prodrug conversion in target versus non-target tissues.

Fundamentally, nothing but hindsight motivates the rejection of claim 10. It is far less trouble to measure prodrug stability in tissue homogenates than in an intact animal, and the examiner has not provided any credible evidence for the assertion that "other variables" would teach or suggest making the change.

In the Advisory Action the examiner replies that the motivation to use intact animals is that intact animals would provide "more information than that performed in a tissue homogenate". It is unclear what this additional information might be to induce one to want to engage in the relatively troublesome step of modifying Shaw et al. to assay individual tissues in an animal, as opposed to homogenates *in vitro*.

The Board is respectfully requested to reverse the examiner's rejection of claims 1, 3-7 and 10-13 over Shaw et al.

The rejection of claims 1, 3 -7, 9 – 13, 15 and 16 under 35 USC 103(a) as unpatentable over Shaw et al. in view of Glazier et al. fails to state a reasonable basis for combining the references, and the combination fails to overcome the deficiencies of Shaw et al.

Glazier et al. discloses cell-permeable prodrugs, accomplished by substituting the phosphorous atoms of parental drugs with a substituted benzyl group (Summary of the Invention). As the examiner has pointed out, Glazier et al. tested activity of the prodrugs in assays using paired infected and uninfected cell lines (col. 36, lines 35-48; col. 37, lines 5 -22

and Cols. 38-39). In particular, the antiviral activity of a given prodrug is tested for example in HBV infected hepatocytes and an uninfected hepatocyte control, and HIV activity was tested in infected and uninfected lymphatic tissue. As an aside, this is relevant to claims 15 and 16 of this case, directed to the use of HIV and HBV activity assays in the method of claim 1.

The examiner urges in the Advisory Action that it would have been obvious to "combine" the screening methods of these references because both are "the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types". The examiner also has taken the position (Office Action mailed Dec. 19, 2006, page 8) that the combination would be desirable because antiviral assays would produce more direct results than the stability assays of Shaw et al. This overlooks the fact that Shaw et al. tested intestine and liver because these are sites of metabolism, not because they are or might be sites of infection. Stated differently, Shaw et al. were conducting a bioavailability study, not an antiviral study, whereas Glazier et al. were conducting an antiviral activity study without any evident concerns for bioavailability. Indirectly measuring bioavailability by measuring antiviral activity would introduce an additional variable into the Shaw et al. study since the presence of the viral infection would constitute an additional variable potentially masking the metabolism of the prodrug. In addition, a straight insertion of the Glazier et al. method into Shaw et al. is anomalous because Glazier et al. discloses no antiviral method using intestinal tissue. There is no reasonable basis to combine Glazier et al. with Shaw et al.

As noted, the examiner apparently believes that the result of the combination would be the bioavailability study of Shaw et al. run with antiviral assays of the sort used by Glazier et al. This would produce antiviral results in different tissues, but since the antiviral assays are for different viruses (each virus for an individual tissue), it would be impossible to compare the *relative* antiviral activities as called for in the claims. In summary, the combination of Glazier et al. and Shaw et al. fails to meet step d) of claim 1, and it fails to remedy the deficiency of Shaw et al. in not setting forth a "target tissue".

Claim 10

Claim 10 is independently patentable over Shaw et al. in view of Glazier et al. for the reasons advanced above.

The Board is respectfully requested to reverse the examiner's rejection of claims 1, 3-7 and 9-13, 15 and 16 over Shaw et al. in view of Glazier et al.

The rejection of claims 1, 3 – 8, 10 – 13 and 17 under 35 USC 103(a) as being unpatentable over Shaw et al. in view of Starrett et al. fails to state a reasonable basis for combining the references, and the combination fails to overcome the deficiencies of Shaw et al.

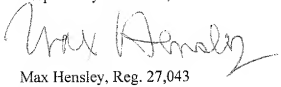
According to the examiner, Starrett et al. teaches administering a PMEA arylester prodrug (PMEA is a methoxyphosphonate nucleotide analogue) to rats and assaying the appearance of the parental drug in urine. PMEA is reported by Starrett et al. to have anti-tumor activity. The examiner points out that Starrett et al. was brought in for its disclosure of the arylester and for its antitumor teaching (relevant to claims 8 and 17). The examiner suggests that it would have been obvious to combine Shaw et al. and Starrett et al. because both are concerned with "bioavailability of prodrugs in animals" (Office Action mailed Dec. 19, 2006). The fact that the references are in the same field does not provide a rationale for the combination. Moreover, even if the references could be combined, Starrett et al. does not teach or suggest any reason for modifying Shaw et al. to assay blood rather than plasma. On the contrary, since Starrett et al. were measuring the PMEA prodrug metabolic products in urine, Starrett et al would suggest modifying Shaw et al. to measure bioavailability in urine, not plasma—much less blood.

Claim 10

Claim 10 is independently patentable over Shaw et al. in view of Starrett et al. for the reasons set forth above.

The Board is respectfully requested to reverse the examiner's rejections of claims 1, 3-13 and 15-17.

Respectfully submitted,



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Claims Appendix

1. A screening method for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue which target and non-target tissues are not the same tissues;

(c) administering the prodrug to the target tissue and to said at least one non-target tissue, provided that said tissues are not in a living human; and

(d) determining the relative antiviral or antitumor activity conferred by the prodrug in the tissues in step (c) wherein the target tissue does not include small intestine.

2. (canceled)

3. The method of claim 1 wherein the activity is antiviral activity.

4. The method of claim 3 wherein the activity is anti-HIV (Human Immunodeficiency Virus) or anti-HBV (Hepatitis B Virus) activity.

5. The method of claim 1 wherein the prodrug is a prodrug of PMPA (9-[2-(phosphonomethoxy)propyl]adenine) or PMEA (9-[2-(phosphonomethoxy)ethyl]adenine).

6. The method of claim 5 wherein the prodrug is a phosphonoamidate, phosphonoester or mixed phosphonoamidate/phosphonoester.

7. The method of claim 6 wherein the phosphonoamidate or phosphonoamidate/phosphonoester is an amino acid amidate.

8. The method of claim 6 wherein the ester is an aryl ester.

9. The method of claim 1 further comprising selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue.

10. The method of claim 1 wherein the target and non-target tissue are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug.

11. The method of claim 1 wherein activity in the target and non-target tissues is determined by assaying the amount of at least one metabolite of the prodrug in the tissues.

12. The method of claim 11 wherein the metabolite is the parental drug.

13. The method of claim 11 wherein the metabolite is the diphosphate of the parental drug.

14. (canceled)

15. The method of claim 1 wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity.

16. The method of claim 1 wherein the target tissue is liver and the activity is anti-HBV activity.

17. The method of claim 1 wherein the target tissue is hematological and the activity is antitumor activity.

18. (canceled)

Evidence Appendix

None

Related Proceedings Appendix

None